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## Aspirin Resistance in Obese and Elderly Patients with COVID-19?



To the Editor:

We read with great interest the recent publication by McCullough et al proposing a comprehensive management strategy for ambulatory patients with coronavirus disease 2019 (COVID-19).<sup>1</sup> The authors should be commended for proposing antiplatelet and antithrombotic therapy early in the disease.<sup>2</sup> McCullough et al recommend 81 mg aspirin daily for high-risk, ambulatory patients with COVID-19.<sup>1</sup> We suggest caution in relying on low-dose aspirin as chemoprophylaxis or treatment for immunothrombosis in COVID-19, especially in patients who are obese or elderly.

Plasma thromboxane B<sub>2</sub> levels are significantly increased,<sup>2</sup> and COX-2 expression is upregulated more than 50-fold in severe COVID-19.<sup>3</sup> COX-2 is inducible and expressed in megakaryocytes and platelets.<sup>4</sup> Low-dose aspirin effectively inhibits COX-1 but not COX-2 activity.<sup>5</sup> Increased expression of cytosolic phospholipase A<sub>2</sub> and COX-2 in the obese or the elderly leads to increased generation of thromboxane A<sub>2</sub> and resistance to aspirin.<sup>6</sup> Among aspirin-naïve subjects, the median urinary 11-dehydrothromboxane B<sub>2</sub> levels was 1433 pg/mg creatinine in the obese compared with 505 pg/mg creatinine in the nonobese, healthy controls ( $P < 0.01$ ).<sup>7</sup> Furthermore, among subjects taking aspirin, serum thromboxane B<sub>2</sub> levels were positively correlated with body mass index (BMI) and body weight, suggesting that thromboxane generation in the obese is COX-2 dependent.<sup>7</sup> The effect of aging on thromboxane generation was studied in 3261 aspirin-treated subjects: the baseline urinary thromboxane B<sub>2</sub> levels increased with advancing age and were associated with higher risk of cardiovascular events (CHARISMA trial).<sup>8</sup> Marked increase in thromboxane generation and COX-2 expression in severe COVID-19 raises the specter of aspirin resistance, especially in patients who are elderly or obese. Though increasingly recommended, the efficacy of low-dose aspirin

remains to be demonstrated in ambulatory or hospitalized patients with COVID-19. The critical role of immunothrombosis in the pathogenesis, progression, and multiorgan failure in COVID-19 underlines an urgent need for effective antithrombotic therapies to reduce the risk of hospitalization, morbidity, and mortality.

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